Committee on Infectious Diseases

The Status of Acellular Pertussis Vaccines: Current Perspective

Clinical studies of component ("acellular") pertussis vaccines have been undertaken in recent years, and several acellular vaccines have been used in Japan for 10 years. The Committee has reviewed these trials and related data and herein provides its assessment regarding the current status of the acellular vaccines and their possible use in the United States.

The pertussis vaccines in current use in the United States are prepared from whole cells of a strain of Bordetella pertussis that is grown in broth medium, harvested by centrifugation, and killed or partially detoxified by heat or by the addition of a chemical agent, such as thimerosal, or by a combination of these methods. In contrast, the acellular vaccines developed in Japan and used in that country since 1981 contain one or more antigens derived from biologically active components of the B pertussis organism. An inactivated form of lymphocytosis promoting factor (LPF), also known as pertussis toxin and a variety of other synonyms, is a frequent component of acellular pertussis vaccines, as are filamentous hemagglutinins (FHA). Other constituents included in acellular vaccines are agglutinogens, a term denoting a variety of protein antigens on the surface of the B pertussis organism. Of the agglutinogens, a 69-kd outer membrane protein, when injected into neonatal mice, protects against B pertussis challenge. Acellular vaccines also have recently been derived from mutant pertussis toxin molecules prepared with recombinant DNA technology.

The acellular vaccines produced in Japan have been classified into two types: B type, which contains LPF and FHA in roughly equal amounts; and T type, which contains mostly FHA but some LPF and agglutinogens. At the present time, no data suggest that the two types differ in the rates of side effects or efficacy.

In Japan, the incidence of pertussis had been declining steadily since the use of whole cell vaccines was mandated by the Preventive Immunization Law of 1948. However, following two post-vaccination deaths in the winter of 1974 to 1975, immunization was suspended temporarily. Two months later, routine immunization with a whole-cell vaccine was reinstated, but the recommended age for administration was changed from 3 months to 2 years of age. Immunizing children at 2 years of age was expected to diminish the occurrence of serious, adverse events temporally related to the administration of the whole-cell vaccine and to protect children younger than 2 years of age against pertussis by preventing transmission of the causative microorganism. Following suspension of pertussis immunization and the ensuing low rates of immunization, the incidence of reported pertussis cases increased dramatically (Fig 1). Subsequently, acellular vaccines were licensed in Japan in 1981 and used for routine immunization of children at 2 years of age. As the acellular vaccines gained acceptance and the vaccination rate increased, reported cases of pertussis declined. This decrease has been interpreted by many experts as evidence of the efficacy of acellular pertussis vaccines. Additionally, a low secondary attack rate in household contacts who have received an acellular pertussis vaccine has been reported. Nevertheless, the rate of reported cases has remained above the rate reported before 1974, primarily because of the continued high incidence of disease in children younger than 2 years of age who were not being immunized in Japan (Fig 2). In an effort to solve this problem,
initiation of acellular pertussis immunization early in the first year of life has been recommended recently by Japanese authorities.

Many investigators have reported that the relatively common, "minor," adverse events occurring after pertussis immunization, such as fever and redness at the injection site, occur less frequently with the use of acellular pertussis vaccines. For example, fever $\geq 38^{\circ}C$ occurred in 25% to 37% of Swedish whole-cell vaccine recipients at 6 months of age, compared with 6% to 8% of recipients of a two-component acellular pertussis vaccine. Redness at the injection site occurred in 24% to 32% and 2% to 13% of whole-cell and acellular pertussis vaccine recipients, respectively. Among 2-month-old children in the United States enrolled in a double-blinded clinical trial with a T-type acellular vaccine, fever was observed in 5% and 38% and erythema at the injection site in 23% and 44% of the recipients of the first dose of acellular pertussis-diphtheria toxoid-tetanus toxoid (ADTP) vaccine and conventional diphtheria-tetanus toxoids-pertussis vaccine, respectively. Importantly, among ADTP recipients, the proportion of children with fever increased with each subsequent dose; and, after a dose of ADTP was given to all children at 18 months of age irrespective of whether they had received three doses of ADTP or whole-cell vaccine previously, 21.2% had fever.

Recently, the efficacy of two acellular vaccines was evaluated in Sweden with the coordinated efforts of investigators from Sweden, the United States, and Japan. This randomized, double-blinded, controlled trial was a study of 3801 children aged 5 to 11 months. The two acellular pertussis vaccines, both developed by the Japanese National Institutes of Health (JNIH), were a B-type vaccine (JNIH-6) that contained equal amounts of LPF (7.5 $\mu g$) and FHA (7.5 $\mu g$) and a monocentric vaccine that contained only LPF (12 $\mu g$) (JNIH-7). Neither vaccine was among the different acellular vaccines routinely used in Japan. Subjects participating in this trial received two doses of either an acellular vaccine or a placebo at an interval of 8 to 12 weeks and were followed up for 17 to 19 months after receipt of the first immunization.

The efficacy of the acellular vaccines in the prevention of pertussis was assessed according to several different case definitions of pertussis. When all "culture-confirmed" cases with a cough of any duration were considered, the efficacy of JNIH-6 and JNIH-7 was 69% and 54%, respectively (Table). However, when the efficacy of the vaccines was based on prevention of culture-confirmed cases with cough lasting more than 30 days, rates of 79%
TABLE. Efficacy of Acellular Pertussis Vaccines in Sweden (Culture-Proven Cases Only)

<table>
<thead>
<tr>
<th>Definition</th>
<th>Vaccine Efficacy (95% Confidence Interval)</th>
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<tr>
<td>Any cough and verified culture of Bordetella pertussis</td>
<td>JNIH-6* 69 (47-82) 54 (26-72)</td>
</tr>
<tr>
<td>Cough &gt;30 days and verified culture of B pertussis</td>
<td>JNIH-7† 79 (57-90) 80 (59-91)</td>
</tr>
<tr>
<td>Spasms (&gt;8/d) and verified culture of B pertussis</td>
<td>JNIH-6* JNIH-7†</td>
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* Contains lymphocytosis promoting factor and filamentous hemagglutinins.
† Contains lymphocytosis promoting factor only.

and 80% for JNIH-6 and JNIH-7, respectively. Based on culture-confirmed cases with more than eight coughing spasms per day, the efficacy of JNIH-6 and JNIH-7 was 85% and 71%, respectively. When pertussis was defined by clinical manifestations only (cough lasting more than 30 days), the efficacy of both vaccines was 78%. Recently, 4-year follow-up data on the prevention of culture-confirmed cases of pertussis by JNIH-6 and JNIH-7 indicated acellular vaccine efficacy ranging from 69% to 95%, depending on the definition of pertussis used, and demonstrated no decline in efficacy during this period.12

A major disappointment in the Swedish vaccine trial was the failure to correlate concentrations of serum anti-LPF and anti-FHA with protection against pertussis after immunization. The absence of a serological correlate relating vaccine immunogenicity to efficacy complicates the evaluation of other candidate acellular pertussis vaccines.

Concern about acellular vaccine safety was raised by the Swedish study. Four subjects died of serious, invasive bacterial infections during the 7- to 9-month period following immunization.13 Three were recipients of JNIH-6 and one received JNIH-7; no deaths occurred among placebo recipients. Many experts doubt that the relationship between the administration of the acellular vaccine and the occurrence of these deaths is more than coincidental. Similar deaths have not occurred in smaller safety trials in the United States. This issue is likely to be resolved with statistical certainty upon analysis of data from larger numbers of immunized children.

In another trial conducted in Sweden, two children who received a two-component acellular pertussis vaccine following initial immunization with whole-cell vaccine developed hypotonia, and another had "persistent and unusual crying."14 The temporal relationship of these events with the antecedent immunization suggests that administration of acellular vaccines to young children may be related coincidentally to those neurological events now temporally related to whole-cell vaccine administration.

The demonstration in Sweden that acellular pertussis vaccines are effective in preventing many cases of pertussis suggests that a similar vaccine might be safe, effective, and suitable for routine use in the United States. However, several important issues require further study. For example, because a whole-cell pertussis vaccine was not included in the Swedish trial, a comparison of efficacy was not possible. Many experts believe that because the vaccines were effective in prevention of culture-proven, clinically significant pertussis, they are comparable to currently used whole-cell vaccines and, thus, are acceptable for routine immunization. However, other experts believe that all cases of pertussis, irrespective of clinical severity, should be preventable by immunization with an acellular vaccine.

Additional questions remain. JNIH-6 and JNIH-7 vaccines were administered in Sweden to 6-month-old children in a two-dose schedule. Will administration to infants 2 months of age be similarly safe and effective? How many doses will be necessary to protect these younger children? Should committees and government agencies involved with public health decision-making in the United States require an efficacy trial in this country prior to the approval of an acellular vaccine? If so, the difficult logistics of conducting a large-scale efficacy trial in this country must be addressed. Which acellular vaccine should be recommended? For example, six vaccines that vary in antigenic content are used in Japan. Which are the important antigens and which antibodies correlate with protection?

Many of these questions will be addressed through current efforts coordinated by the National Institute of Allergy and Infectious Diseases. Currently, at least 12 candidate acellular and recombinant pertussis vaccines are undergoing evaluation for safety and immunogenicity, and one or more of these vaccines will be used in an efficacy trial scheduled to begin in late 1991. All candidate vaccines contain pertussis toxoid, whether native or recombinant; some also contain FHA, agglutinogens, the 69-kd outer membrane protein, or a combination of these antigens. Because the severity of pertussis is inversely related to age at presentation, the goal should continue to be the identification of an acellular or recombinant pertussis vaccine with minimal associated adverse events and at least equal effectiveness to that of current whole-cell
vaccines in preventing disease when immunization is initiated at 2 months of age.

Fewer questions, however, remain regarding the use of an acellular vaccine in children previously immunized with whole-cell vaccine. Because the severity of pertussis diminishes with increasing age, the benefits of acellular pertussis vaccines with fewer minor adverse reactions outweigh the uncertainties about their efficacy when given as booster doses after initial whole-cell immunization in infancy. The evidence from the epidemiological experience in Japan, the results of the Swedish trial, and the serological responses of 17- to 24-month-old recipients of one candidate acellular vaccine in the United States suggest that an acellular vaccine could replace whole-cell vaccine for routine administration at 15 to 18 months and at 4 to 6 years of age in the United States. Serious consideration of acellular pertussis vaccine for the routine fourth and fifth doses is warranted.

SUMMARY AND RECOMMENDATIONS

1. The present strategy in the United States of administering three doses of whole-cell pertussis vaccine in early infancy with additional doses at 15 to 18 months and 4 to 6 years of age effectively prevents pertussis. The uniform occurrence of epidemic pertussis in every country that temporally has abandoned routine pertussis immunization underscores this fact.

2. The Swedish trial and the experience in Japan have provided evidence that acellular vaccines can prevent pertussis with fewer local and systemic reactions than with whole-cell vaccine.

3. Additional efficacy data are needed before one or all of the acellular vaccines can be recommended for routine use in this country during early infancy.

4. The Academy believes that one or more of the acellular pertussis vaccines already used widely in Japan should be considered for introduction in the United States as an alternative to the whole-cell vaccine normally administered at 15 to 18 months of age and at the time of school entry.

REFERENCES


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